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CORRESPONDENCE

Letters to the Editor

Spontaneous Late Closure of Patent Foramen Ovale

The study by Meissner et al. (1) and the accompanying editorial by Meier (2) provide contrasting views concerning the pathologic significance of patent foramen ovale (PFO). A large autopsy study from the Mayo Clinic (3) showed a decreasing incidence of PFO with age that the investigators attributed to late spontaneous closure, although they did not suggest the mechanism whereby this might occur. Meier (2) proposes an alternative explanation, namely that the presence of a PFO is associated with a reduced life expectancy. Meissner et al. (1) and Siostrzonek et al. (4) note that a PFO is less frequently detected in patients with elevated left atrial pressure, but they imply that this is the result of a lower sensitivity of the detection technique rather than a lower incidence of PFO.

We believe it unlikely that a PFO confers a significant mortality disadvantage. If this were the case then one would expect a lower proportion of larger PFOs with age as large PFOs are considered to confer a higher risk of adverse events (2). Hagen et al. (3) found the reverse. We believe a more plausible explanation is that a chronically elevated left atrial pressure as occurs with advancing age and loss of left ventricular compliance (5) can result in late closure of a PFO, particularly if small. Indirect evidence for this assumption comes from an observation that in a personal series (R.W.H.) of 260 consecutive patients with mitral stenosis undergoing percutaneous trans-septal valvuloplasty, a PFO was crossed only twice. In this procedure the foramen ovale is always probed with a catheter stiffened with the trans-septal needle. Accordingly, if a PFO had been present in these patients with the same incidence as in the general population (25%), one would have expected a much higher crossing rate than was observed (<1%). In an otherwise normal heart it is generally very easy to cross a PFO with a catheter directed at the limbus of the fossa ovalis.

We believe that the likely explanation for the low crossing rate in mitral stenosis is that the chronically elevated left atrial pressure associated with this condition results in closure of a PFO. We also believe that the lower detection rate of PFO in conditions with elevated left atrial pressure may be the result of late closure of the PFO rather than an inability to detect the condition.

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Patent Foramen Ovale and the Risk of Cryptogenic Stroke

We would like to congratulate Meissner et al. on their impressive cohort study of patent foramen ovale (PFO) and stroke. However, we hold significant reservations on the stated conclusion that PFO is not an independent risk factor for future cerebrovascular events in the general population (1).

The population studied by Meissner et al. (1) was predominately elderly, with a mean age of nearly 70 years (± 13 years). The association of PFO and stroke is much less conclusive in older populations, with conflicting studies (2,3). Increasing age is associated with increasing incidence of traditional risk factors for atheroembolic stroke—clearly demonstrated in this study where over 50% of subjects were hypertensive and over 50% had visible aortic plaque (1). It is likely that mechanisms other than paradoxical embolism predominate in these older age groups. The plausibility of a congenital defect suddenly causing a cerebrovascular ischemic event is intuitively much less.

Additionally, it appears no attempt was made to identify those ischemic strokes that were considered "cryptogenic." These represent the minority of the total strokes (4), but they have been most often associated with PFO (5).

The management of PFO and cryptogenic stroke is an evolving area (6). There are currently at least 3 recruiting trials of PFO closure versus medical management. Of note, all specify an upper age limit for enrollment of 60 years (7–9). The results of these trials are eagerly awaited.

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REPLY

The comment by Harper and Haqqani, namely that a patent foramen ovale (PFO) is unlikely to confer a significant mortality disadvantage, indirectly acknowledges that it might. Paradoxical embolism through a PFO can unequivocally have devastating consequences, including death. Hence, even if no significant risk for mortality has yet been proven, people die from it (1). This must suffice to take the matter seriously. If there was a simple vaccination to close the PFO, it would be a world standard. Implantation of a device in the heart, with an inherent risk for mortality as well, needs proof of superiority over the natural course. This proof (or disproof) is subject to time. About 1,000 patients have been randomized between device closure and natural course in a variety of trials in progress. Device implantation should show any disadvantage quite early as its risks are front-loaded. An advantage, however, takes many years to unveil because events from a PFO are fortunately rare (rarer than we initially thought), but not absent. None of the trials has been stopped prematurely, which speaks against a disadvantage without compromising the hope for an advantage of PFO closure.

The theory of selective mortality of the PFO is indeed not in keeping with the finding that the fewer PFOs in the elderly are larger in size (2). The theory of late spontaneous fusion by increasing left atrial pressure with age could explain that. Conversely, there is hard evidence for the first theory (people do die from PFOs) but not for the second. The fact that patients with mitral stenosis had a passable PFO in <1% according to Harper and Haqqani is not sufficiently explained by either theory. The bulging of the atrial septum into the right atrium in mitral stenosis is likely to render catheter passage from the inferior vena cava more difficult as the PFO is hidden behind this bulge in a region where the septum now is tangential to the catheter path, making probing for the PFO unyielding. Many PFOs go undetected under these circumstances, although they are not fused but simply functionally closed by elevated left atrial pressure and moved out of target for access from the inferior vena cava.

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REPLY

We appreciate and acknowledge the interest in our recently reported study (1). In regard to the comments of Schrale et al., we studied subjects in age increments or "cells" of 10 years beginning at age 45, and we did not find an increased stroke risk in even the younger age cells. A recent case control study published by Petty et al. (2) supports our finding that patent foramen ovale (PFO) does not appear to be a risk factor for cryptogenic stroke in the general population.

Also, Harper and Haqqani provide intriguing thoughts regarding the issue of PFO detection rates in older individuals. It is possible that a PFO may close in older subjects, but this postulate is based on many assumptions, including that older people have elevated left atrial pressures. This is an interesting concept that merits systematic evaluation.

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Coronary Plaque Burden and Cardiovascular Risk Factors: Single-Point Versus Serial Assessment

In their interesting study, Nicholls et al. (1) recently assessed in a large series of patients the relation between various cardiovascular risk factors and the amount of coronary plaque burden with (*non-serial*) volumetric intravascular ultrasound (IVUS). In this set of high-quality data, male gender, diabetes mellitus, and a history